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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,014	04/19/2001	Crystal C. Watkins	55802 (71699)	3068

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EXAMINER
RUSSEL, JEFFREY E

ART UNIT	PAPER NUMBER
1654	9

DATE MAILED: 01/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/840,014	Applicant(s) WATKINS ET AL.	
	Examiner Jeffrey E. Russel	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2002 and 22 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,13-20,24,25,29,35,42-44,49,51 and 53-56* is/are pending in the application.

4a) Of the above claim(s) *2,15,16,18,42,43 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,13,14,17,19,20,24,25,29,35,44,51 and 53-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. It should be noted that the originally-presented claim numbered "57" has been re-numbered as "56" under 37 CFR 1.126. This was done so that all claims presented in the application have been numbered consecutively. Any future reference to this claim will use its re-numbered claim number. Should Applicants present any new claims in any response filed in this application, the new claims should be numbered beginning with "57".

2. Applicant's election with traverse of the species sildenafil in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the election of species requirement contains no evidence and explanation why examining the claims presents a serious burden. This is not found persuasive because the evidence and explanation is set forth at page 2, lines 4-8, of the election requirement. In any event, the proper traversal to a requirement for election of species is the submission of evidence or an argument that the species are not patentably distinct or are obvious variants of each other. See the Office action mailed October 1, 2002, page 3, lines 1-5. Applicants have not submitted any such evidence or made any such admission.

The requirement is still deemed proper and is therefore made FINAL.

Apparently in response to the requirement to list all claims readable on the elected species (see page 2, lines 13-15, of the Office action mailed October 1, 2002), Applicants state that "each pending claim embraces this genus". However, the requirement was to list all claims which embrace the elected species, i.e. sildenafil. Claims 2, 15, 16, 18, 42, 43, and 49 do not embrace the elected species.

At page 2, lines 1-2, of Applicants' response, Applicants request that if the examiner maintains the rejection, that he examine a reasonable number of species as promised. Firstly, the Office action mailed October 1, 2002 sets forth an election of species requirement and does not

contain any rejection of any claim. Secondly, the examiner did not promise to examine a reasonable number of species. Rather, the procedure is that if the elected species is searched and found to be novel and unobvious, the examiner will extend the search to the remainder of the genus.

Claims 2, 15, 16, 18, 42, 43, and 49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> It does not identify the citizenship of each inventor.
> It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

The declaration filed January 28, 2002 and signed by inventor Ferris does not include the city of residence. The declaration filed January 28, 2002 and signed by inventors Watkins and Snyder does not include any residence or post office address data, and does not include the citizenship of each inventor.

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Errors which have been noted by the examiner are: At page 18, line 9, the third patent number in the line is incomplete. At page 18, line 11, the period within the patent number should be changed to a comma. At page 98, line 23, "gastric" is misspelled.

5. Claims 25, 35, 44, and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 25, 35, and 44 are indefinite because they are incomplete. These claims refer to the specification for Formulae I through XIII rather than recite them explicitly in the claims. Applicants have not shown that there is no other practical way to define the invention in words, i.e. by explicitly reciting the Formulae in the claims. See MPEP 2173.05(s). To the extent that the claims incorporate by reference the definition of Formula II set forth in the specification, the claims are indefinite because the variable R^1 is not defined for Formula II. To the extent that claims 25, 35, and 44 incorporate by reference the definition of Formula VII set forth in the specification, the claims are indefinite because it is not clear if the solvates referred to at page 27, line 17, are to be limited to hydrates or not. It is suggested that the parenthetical phrase could be deleted and made the subject matter of a further dependent claim. For analogous reasons with respect to the solvates and hydrates, Formulas VIII-XII are also indefinite. For analogous reasons with respect to halogen and fluorine, and with respect to "especially hydrogen", Formula IX is indefinite. The use of the trademark "Viagra" in claim 29 is indefinite because Applicants are using the trademark to identify a particular material or product, whereas a trademark defines the source of a particular material or product and not the material or product itself. See MPEP 2173.05(u). It is recommended that the trademark "Viagra" in claim 29 be replaced with the generic terminology "sildenafil".

6. Claims 25, 35, 44, and 51 are objected to because of the following informalities: At claim 25, line 2, "any one" should be two words. To the extent that claims 25, 35, and 44 incorporate by reference the definition of Formula II set forth in the specification, the claims are objected to because the phrase "pharmaceutically salts" (see page 20, line 6) is non-grammatical and appears to be missing the word "acceptable". To the extent that claims 25, 35, and 44 incorporate by reference the definition of Formula VI set forth in the specification, the claims are objected to because the numeral "8" should be a subscript (see page 26, lines 5 and 6), and because the word "of" should be changed to "or" (see page 26, line 18), and because "and" should be changed to "acceptable" (see page 26, line 19, second occurrence). To the extent that claims 25, 35, and 44 incorporate by reference the definition of Formula VII set forth in the specification, the claims are objected to because the numeral "8" should be a subscript (see page 27, line 5). To the extent that claims 25, 35, and 44 incorporate by reference the definition of Formula X set forth in the specification, the claims are objected to because the numeral "8" should be a subscript (see page 35, lines 7 and 8) Appropriate correction is required.

7. Instant claims 1, 3-7, 13, 14, 17, 19, 20, 24, 25, 29, 35, 44, 51, and 53-56 are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/198,545 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, does not disclose treating mammals susceptible to (as opposed to suffering from) a gastrointestinal disorder; does not disclose treating a mammal which has been identified and selected for treatment to increase the nNOS level; does not disclose all of the disorders recited in instant claims 5-7, 13, 44, 51; does not disclose administering a compound that boosts insulin effects or levels in conjunction with a PDE inhibitor; does not disclose all of the active agents of

Formulae I through XIII; does not disclose preventing diabetic gastropathy; and does not disclose the administration of prokinetic agents in general. In general, see MPEP 201.11 under "When Not Entitled To Benefit Of Filing Date".

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

9. Claims 1, 3-7, 14, 17, 19, 20, 25, 29, 44, 51, and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by the Bortolotti et al article (Gastroenterology, Vol. 118, pages 253-257). The Bortolotti et al article teaches treating patients with achalasia where there is an impairment of nitric oxide poduction by administering sildenafil, which blocks a phosphodiesterase type 5 that destroys nitric oxide-stimulated cGMP. See, e.g., the Abstract.

10. Claims 1, 3-7, 14, 17, 19, 20, 25, 29, 35, 44, and 51 are rejected under 35 U.S.C. 102(a) as being anticipated by the Watkins et al abstract (Gastroenterology, Vol. 118, No. 4, Suppl 2, page A669, Abstract 3667). The Watkins et al abstract teaches treating diabetic mice with diabetic gastropathy by administering sildenafil and zaprinast. The mice are identified as having reduced nNOS expression.

11. Claims 1, 5-7, 14, 17, and 53 are rejected under 35 U.S.C. 102(e) as being anticipated by Cutler et al (U.S. Patent No. 6,451,813). Cutler et al teach administering flosequinan and cilostazol, which are phosphodiesterase inhibitors, to humans, including humans with diabetes, with gastroparesis. See, e.g., the Abstract; column 9, lines 41-43; and column 10, lines 26-27 and 34-36. With respect to instant claims 1 and 17, in view of the similarity in function and effect between the active agents of Cutler et al and Applicants' claimed active agents, the active agents of Cutler et al are deemed inherently to be capable of increasing nitric oxide activity as measured in a standard gastric emptying assay. Note that the claim does not specify any

particular assay and does not specify any degree of increase. Sufficient evidence of similarity is deemed to be present between the method of Cutler et al and Applicants' claimed method to shift the burden to Applicants to provide evidence that the claimed method is unobviously different than that of Cutler et al. Note that the mere determination of the exact physiological mechanism by which a known treatment method operates does not impart patentability to claims drawn to the known treatment method. See In re Skoner, 186 USPQ 80, 82 (CCPA 1975).

12. Claims 1, 5-7, 14, 17, and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Stief et al (U.S. Patent No. 5,891,904). Stief et al teach administering a phosphodiesterase inhibitor in order to modulate the motility and peristalsis of the hollow organs of the urogenital and gastrointestinal tract. Administration can be oral. See, e.g., the Abstract; column 2, lines 2-5; column 3, lines 1-6 and 44-61; and claims 1-4. With respect to instant claims 1 and 17, in view of the similarity in function and effect between the active agents of Stief et al and Applicants' claimed active agents, the active agents of Stief et al are deemed inherently to be capable of increasing nitric oxide activity as measured in a standard gastric emptying assay. Note that the claim does not specify any particular assay and does not specify any degree of increase. Sufficient evidence of similarity is deemed to be present between the method of Stief et al and Applicants' claimed method to shift the burden to Applicants to provide evidence that the claimed method is unobviously different than that of Stief et al. Note that the mere determination of the exact physiological mechanism by which a known treatment method operates does not impart patentability to claims drawn to the known treatment method. See In re Skoner, 186 USPQ 80, 82 (CCPA 1975).

13. Claims 1, 3-7, 14, 17, 19, 20, 25, 44, 51, and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by the European Patent Application 656,898. The European Patent Application '898 teaches inhibitors of cGMP phosphodiesterases (i.e. PDE5) which as a result potentiate the effects of EDRF (i.e. nitric oxide). The inhibitors are administered to patients in order to treat diseases characterized by disorders of gut motility, e.g., irritable bowel syndrome. See, e.g., page 2, lines 6-14 and claim 7.

14. Claims 1, 3-7, 14, 17, 19, 20, 25, 29, 35, 44, 51, and 53 are rejected under 35 U.S.C. 102(e) as being anticipated by Gmunder et al (U.S. Patent Application Publication No. 2002/0012633). Gmunder et al teach the administration of sildenafil citrate in chewing gum form to treat esophageal spasms, dysphagia, and gastroparesis associated with diabetes. See, e.g., the abstract and paragraph [0088].

15. Claims 1, 5-7, 13, 14, 17, 25, 44, 51, and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Warrellow et al (U.S. Patent No. 5,859,034). Warrellow et al teach the use of phosphodiesterase inhibitors to treat inflammatory diseases such as ulcerative colitis and Crohn's disease. Oral administration is taught. See, e.g., column 10, lines 37-60, and claims 14 and 16. With respect to instant claims 1 and 17, in view of the similarity in function and effect between the active agents of Warrellow et al and Applicants' claimed active agents, the active agents of Warrellow et al are deemed inherently to be capable of increasing nitric oxide activity as measured in a standard gastric emptying assay. Note that the claim does not specify any particular assay and does not specify any degree of increase. Sufficient evidence of similarity is deemed to be present between the method of Warrellow et al and Applicants' claimed method to shift the burden to Applicants to provide evidence that the claimed method is unobviously

different than that of Warrellow et al. Note that the mere determination of the exact physiological mechanism by which a known treatment method operates does not impart patentability to claims drawn to the known treatment method. See In re Skoner, 186 USPQ 80, 82 (CCPA 1975).

16. Claims 54-56 are rejected under 35 U.S.C. 103(a) as being obvious over the Bortolotti et al article (Gastroenterology, Vol. 118, pages 253-257) as applied against claims 1, 3-7, 14, 17, 19, 20, 25, 29, 44, 51, and 53 above, Cutler et al (U.S. Patent No. 6,451,813) as applied against claims 1, 5-7, 14, 17, and 53 above, Stief et al (U.S. Patent No. 5,891,904) as applied against claims 1, 5-7, 14, 17, and 53 above, Gmunder et al (U.S. Patent Application Publication No. 2002/0012633) as applied against claims 1, 3-7, 14, 17, 19, 20, 25, 29, 35, 44, 51, and 53 above, or Warrellow et al (U.S. Patent No. 5,859,034) as applied against claims 1, 5-7, 13, 14, 17, 25, 44, 51, and 53 above, and further in view of Benet et al (U.S. Patent No. 6,004,927). The Bortolotti et al article, Cutler et al, Stief et al, Gmunder et al, and Warrellow et al do not teach co-administration of their orally-administered active agents with a prokinetic such as erythromycin. Benet et al teaches co-administration of orally administered drugs, including pyrimidines and sulfones, with cytochrome P450 3A enzyme inhibitors or with inhibitors of P-glycoprotein-mediated membrane transport, in order to enhance the bioavailability of the drug after oral administration. Erythromycin is given as an example of such an inhibitor. See, e.g., the Abstract; Tables 1 and 2; and claims 12 and 18. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to co-administer the inhibitors of Benet et al, such as erythromycin, with the active agents of the Bortolotti et al article, Cutler et al, Stief et al, Gmunder et al, or Warrellow et al because the active agents can be administered

orally and because co-administration with the inhibitors of Benet et al would improve the bioavailability of the active agents.

17. Claims 1, 4-7, 14, 17, 19, 20, 24, and 53 are rejected under 35 U.S.C. 102(e) as being anticipated by Michaeli (U.S. Patent No. 6,417,208) in view of Dorziotis et al (U.S. Patent No. 5,856,498). Michaeli teach the co-administration of phosphodiesterase 1C inhibitors, such as zaprinast, with insulin or sulfonylureas in order to treat diabetes. See, e.g., column 5, lines 23-35, and column 10, lines 37-49. Dorziotis et al teach that zaprinast is a PDE V inhibitor. See column 1, lines 28-29. Because zaprinast is a PDE 5 inhibitor, it would have been expected inherently to augment nitric oxide production as measured in a gastric emptying assay and to increase cGMP as measured by a standard cGMP assay because these are properties possessed by the class of PDE 5 inhibitors. The diabetic patients treated by Michaeli are inherently susceptible to gastrointestinal disorders. Accordingly, the method of Michaeli inherently treats diabetic patients susceptible to gastrointestinal disorders with a combination of a PDE 5 inhibitor and known antidiabetic drugs including insulin and sulfonylurea.

18. The Eherer et al abstract (Gastroenterology, Vol. 118, No. 4, Suppl. 2, pages A626-A627, Abstract 3207) and the Bortolotti et al abstract (Gastroenterology, Vol. 118, No. 4, Suppl. 2, Abstract 4770) are cited as art of interest, but are deemed essentially duplicative of the Bortolotti et al article applied above. The Watkins et al abstract (Society For Neuroscience Abstracts, Vol. 30, Part 2, page 1435, Abstract 537.1) is cited as art of interest, but is deemed essentially duplicative of the Watkins et al abstract applied above.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.

Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

January 3, 2003